PHARMACEUTICAL INSPECTION CONVENTION

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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AIDE-MEMOIRE

INSPECTION OF MEDICINAL GASES

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1. DOCUMENT HISTORY

Adoption by Committee	30 May 2006
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2. INTRODUCTION

2.1 Manufacturing of medicinal gases is regulated by the PIC/S GMP Guide and Annex 6. The last revision of Annex 6 was done in 2001 (entry into force: September 2001). In 2003, the PIC/S Expert Circle on Medicinal Gases established a Working Group in order to draft an Aide-Memoire on the Inspection of Medicinal Gases.

2.2 As the industrial production of gases is commonly a highly automated, continuous process, involving automated systems, emphasis must be put on investigating this aspect during an inspection. It requires a detailed technical knowledge, including insight of computerised systems (see specific PIC/S guidance), from GMP inspectors.

2.3 The manufacture of medicinal gases is a process carried out in closed equipment. However, the re-use of containers without adequate precautions could lead to a contamination of the product by a wide variety of contaminants.

3. PURPOSE

This Aide-Memoire was prepared to enable the effective planning and conducting of GMP inspections of manufacturing of medicinal gases, in particular from the point of view of optimal use of limited inspection time and from the point of view of optimal evaluation of GMP compliance.

4. SCOPE

This document describes three different types of manufacturing of medicinal gases: air separation units, filling stations and manufacturing of medicinal gases in hospitals which should be covered during inspections and which should be evaluated from the point of view of GMP compliance. This document focuses on the special needs for inspecting the manufacturing of medicinal gases.

	Area of operation/Items	Items	Crucial questions	Supporting documents

5. AIDE MEMOIRE

1.	**General**			
1.1		▪ Manufacturing authorisation (if any)	▪ API/bulk/manufacturing at the hospital?	National legislation
1.2		▪ Site Master File (if any)		PIC/S recommendation
1.3	Personnel	▪ Organisation chart	▪ Personnel? ▪ Defined responsibilities? ▪ Responsible persons?	GMP Chapter 2 GMP Annex 6: 2
1.4	Personnel	▪ Qualification and training of personnel	▪ Are training needs identified? ▪ Training records? ▪ Is training effectiveness assessed?	GMP Chapter 2 GMP Annex 6: 2.2 GMP 2.9
1.5	**Quality management**	▪ QA/QC systems	▪ Complaints? ▪ CAPA? ▪ Deviations? ▪ Change control?	GMP Chapter 1
		▪ Self Inspection	▪ Is there a procedure? ▪ Is there a schedule?	GMP Chapter 1.2 and 9
	Contract manufacture. and analysis	▪ Contracts	▪ Is there any outsourcing, including container testing, transportation? ▪ Accepting and auditing policy?	GMP Chapter 7
	Validation / Qualification	▪ Qualification ▪ (DQ,IQ,OQ,PQ) ▪ VMP ▪ Revalidation ▪ Computerised systems ▪ Risk analysis ▪ Process validation ▪ Change Control	▪ Validation policy of the factory/hospital? ▪ Are critical control points identified? ▪ Are critical processes validated and critical equipment qualified? ▪ Timetable if not implemented and present validation status? ▪ Periodically system review ▪ GMP critical Computerised systems validation policy? (controlling / monitoring) ▪ Cylinder cleaning validated?	GMP Annex 15 GMP Annex 6: 5.1 and Annex 11 GMP Annex 6: 5.3.6
	Validation	▪ Analytical methods	▪ Are analytical methods appropriately validated?	
	Complaints and product recall	▪ Complaints, recall	▪ How often do customers query empty containers? ▪ How this deficiency is classified?	GMP Chap. 8 and point 5.1.

	Area of operation/Items	Items	Crucial questions	Supporting documents
	Premises	▪ Preventative maintenance of filter(s), compressor, cooler and separation column, storage tank(s), pipelines	▪ Plant, process, calibration system?	GMP Chap. 3
	Container design	▪ Containers suitable for medicinal gases	▪ Valve specific for a particular gas or mixture of gases? ▪ Risk of contamination in the case of complete emptying? ▪ Possibility and methods of cleaning?	
1.6	Premises	▪ Remote operation of ASU ▪ List of products	▪ Are there controls to prevent access by unauthorised persons? ▪ Separation of medical technical/industrial gases?	GMP 3.6 GMP Annex 6: 3.1.1and 3.1.2

Air separation unit [oxygen (and nitrogen) only]

2.	**Air separation units Production**			GMP Annex 6: 5
2.1		▪ Batch definition	▪ How do they define the batch? Criteria used to define a batch?	GMP Annex 6: 5.2.7
2.2		▪ Flow chart of the process ▪ Layout of the plant, line drawings ▪ Shutdown and start-up	▪ Rational explanation on procedure? ▪ Which are the critical points of the process? ▪ Where and how samples of products and intermediates are taken? ▪ How do you clean and purge?	GMP Annex 15
2.3		▪ **Air Inlet** - Position - Is it regularly cleaned - Sequence of filters (dust, CO2, water, hydrocarbons)	▪ What is the quality of the air? ▪ Potential Contaminants near by?	GMP Annex 6: 5.2.2 GMP 4.11
2.4		▪ **Filters & /Molecular Sieves** - Types - Changing frequencies - Proper installation - For sieves regeneration - Pressure drop - Integrity testing	▪ What type of filters do they use? ▪ SOP for maintenance? ▪ How is (or is) really integrity tested for these filters?	GMP Annex 6: 5.2.4

	Area of operation/Items	Items	Crucial questions	Supporting documents
2.5		▪ **Air compressors** - Maintenance frequency - Change and consumption of oil - Oil type used - Check of bearings - Air Cooled - Water cooled (water quality) - Pressure	▪ Type of compressor and oil used? ▪ If water could come in contact with medicinal gas: microbiology?	GMP Chap. 3 GMP Annex 6: 5.2.9
2.6		▪ **Separation column** - Proper design (valves, sensors) - Maintenance - Removal of contaminants - Pressure - Liquid levels	▪ Removal of contaminants (e. g. Argon?) ▪ Checking of important parameters? (temperature, pressure)	GMP Chap. 3 GMP Annex 6: 5.2
2.7		▪ **Storage tank** - Design - Maintenance - Tank pressure - Filling level		GMP Chap. 3 GMP Annex 6: 5.2
2.8	Transport process for bulk gases	▪ Transport process for bulk gases • Bulk transport • Filling and decantation procedure • Dedicated Mobile delivery tank • Storage tank	▪ Is there a qualification report for mobile and stationary storage tank? ▪ Are the mobile tank and the storage tank dedicated to medicinal gas? ▪ Identification of filling points and methods for prevention of incorrect connections? ▪ What is your bulk concept in relation to mobile tanks?	GMP Annex 15 GMP Annex 6: 3.2.1
2.9	In Line Process Monitoring	E. g. In line gas analyzers	▪ Records from dedicated in line process monitoring equipment? ▪ Is there a critical instrument list? ▪ Are there procedures for calibration of critical instruments such as analyzers? ▪ Have appropriate calibration tolerances been applied?	GMP 5.48 GMP 3.41 GMP Annex 6: 3.2.1

	Area of operation/Items	Items	Crucial questions	Supporting documents
3.	**Air separation units** **Quality control**			GMP Annex 6: 6
3.1		Specifications for finished products		Ph Eur
3.2	Quality control labs	▪ Test method ▪ Trend analysis ▪ Validation of analytical methods ▪ Tubing distance for sampling and purging principles when performing analysis ▪ Calibration gases ▪ Standards ▪ Microbiological contamination ▪ Particles ▪ OOS	▪ Raw data? ▪ Suitability of the method? ▪ Has this equipment set up been validated? ▪ Is the point of measurement sufficiently close to the gas source to ensure steady state conditions during analyses? ▪ Is there a certificate of analysis available for the reference gases used?	GMP Annex 15
3.3		▪ Release	▪ How and who is responsible? ▪ Verify products not released!	GMP Annex 6: 2.1 and 7.1
4.	**Air separation units** **Documentation**		▪ The syntax of all these documents?	GMP Chap. 4
4.1		▪ Master batch doc		
4.2		▪ Certificate of analysis		
4.3		▪ Relevant SOPs		
4.4		▪ Logbooks for equipment		

Filling station

5.	**Filling station**			
5.1	Supplier of the bulk	▪ Bulk gases	▪ Types of bulk gases? ▪ Agreements? ▪ Requirements for transport (contract, dedicated) tanks? ▪ Procedures for loading and documentation?	GMP Annex 6: 5.2.10
5.2	Control of the incoming bulk	▪ Unloading procedure ▪ Definition of batch ▪ Requirements for documentation ▪ Quality control (testing) ▪ Release of bulk ▪ Delivery documents	▪ Procedures for unloading and documentation? ▪ When? ▪ How are deliveries of gases outside of normal working hours handled? ▪ Presence of staff? ▪ Who can unload?	GMP Annex 6: 5.2.10/11

	Area of operation/Items	Items	Crucial questions	Supporting documents
			▪ How hoses are handled? ▪ What controls are required for unloading? ▪ QC on delivery vessel or on bulk tank? ▪ C of A? ▪ Delivery points protected when not in use?	
5.3	Cylinders	▪ Ownership and types of cylinders	▪ Who owns the cylinders and the valves? ▪ Who releases the containers for the filling? ▪ Valves; type – including pressure retention valves? ▪ Traceability of valves - batch number of valves/ changing documentation?	GMP Annex 6: 5.3
		▪ Receiving and preparation	▪ How are cylinders handled upon receipt? ▪ Are the cylinders returned by the customer checked for open valves to avoid the risk of contamination during storage and transportation? ▪ Receiving of empty cylinders: new/ used ones/ return after maintenance? ▪ External appearance? ▪ Valves: open or not? ▪ Do you check the residual pressure? ▪ Procedure with/ without residual pressure? ▪ Are there internal visual inspection followed by cleaning with validated methods in the case of cylinders without residual pressure? ▪ Do the additional measures for empty cylinders make sure that there is no contamination with water or other contaminants?	
		▪ Maintenance	▪ How are the cylinders prepared? (connected,	

	Area of operation/Items	Items	Crucial questions	Supporting documents
			relabelled, evacuation, purging) ▪ When and where are old labels removed? ▪ Washing? ▪ Who is responsible for their maintenance? ▪ Maintenance records? ▪ What requirements for maintenance (hydrostatic test, pressure testing, painting, rust, valves)? ▪ Frequency and how managed? ▪ Maintenance outsourced? ▪ Hydrostatic pressure test : quality of the water used ▪ Internal inspection?	
		▪ Storage ▪ Specification for cylinders and valves	▪ New cylinders (or cylinders coming from hydrostatic pressure test): who is responsible for internal inspection? When and how? ▪ How are cylinders re-commissioned after maintenance? ▪ Storage of empty and filled cylinders (storage, protection, quarantine) ▪ Are returned cylinders, prepared cylinders and full cylinders adequately segregated? ▪ Specification for cylinders and valves? Specifications for the quality of inner surface (rust, corrosion, roughness)?	
		▪ Cleaning validation	▪ Is there a validation report? ▪ Is there an adequate risk analysis taking into account all impurities probable in the case of returning cylinders with open valves / without residual pressure (e.g. rust, dust, residuals of liquid contamination)?	
		▪ Valves	▪ Is there an adequate protection against contamination during	GMP Annex 6: 7.4

	Area of operation/Items	Items	Crucial questions	Supporting documents
			transport? ▪ Are valves gas specific? ▪ Tamper evident seals? ▪ Maintenance of valves: method, frequency and documentation?	GMP Annex 6: 5.3.3
		▪ Traceability	▪ Is there a system to secure traceability of cylinders, valves, gases and filling?	GMP Annex 6: 5.3.3
5.4	Premises and equipment	▪ Layout, suitability	▪ Is design suitable for medicinal gases? ▪ Industrial/medicinal separation? ▪ Access to the filling area and storage area?	GMP Annex 6: 3.1.1 and 3.2.4
			▪ Measures for the prevention of the connection of wrong containers?	GMP Annex 6: 3.2.2
			▪ Segregation of the different gases, cylinders, and of gases at different stages of processing?	GMP Annex 6: 3.1.3
			▪ How are the areas marked? Identification?	GMP Annex 6: 3.1.3
			▪ Pipelines; where, dedicated, back-flow valves (to QC, mixing) labelling?	GMP Annex 6: 3.2.4
		▪ Contamination	▪ Maintenance (evaporators, tanks, flow-meters, pressure indicators, alarms, balances, pumps)?	GMP 3.34
			▪ Calibration of equipment?	GMP Annex 6: 3.2.1
			▪ Adequate measures to prevent contamination of the manifold/ filing line?	
			▪ Control of cleaning and purging of filling equipment and pipelines including checks for absence of contaminants? Records?	GMP Annex 6: 5.3.4
			▪ How do you avoid contamination of the manifold / filling line with the content of cylinders which have been returned for refilling?	

	Area of operation/Items	Items	Crucial questions	Supporting documents
5.5	Filling process	Filling	▪ How is a batch defined? ▪ Is there a line clearance before starting filling? ▪ How is filling controlled (weight, flow/time, pressure, feel with hand)? ▪ If fill controlled by pressure is settle pressure measured? ▪ How are mixed gases filled? ▪ Mixing procedure for mixed gases (validation, rolling/tumbling)? ▪ What in process controls are there (especially mixed gases)? ▪ For multi-cylinder manifolds – how do you ensure every cylinder is filled? ▪ Sealing procedure (tamper evidence)? ▪ Labelling/ content of label/ reconciliation/ instruction for use? ▪ How are batch labels prepared and applied? ▪ How are cylinder bundles, homecare, mobile containers filled?	GMP Annex 6: 5.3 GMP 5.45
		Traceability	▪ How do you check leakage? ▪ Batch documentation (what, when, how, by whom), gas batch, cylinders?	GMP Annex 6: 4.1
5.6	Quality control	▪ Testing of bulk gas	▪ At what points are samples withdrawn i.e. from the tanker prior to delivery into the storage tank? ▪ Specs? ▪ What is the extent of testing performed? ▪ Is bulk gas released before filling into the cylinders?	GMP Annex 6: 6
		▪ Testing of final product ▪ Test methods	▪ What is the sample size (sampling plan) for filled cylinders? ▪ How is testing done and by whom?	

	Area of operation/Items	Items	Crucial questions	Supporting documents
		▪ Quarantine (physical, administrative) ▪ Release	▪ Specifications? ▪ Documentation and evaluation of results (sign.)? ▪ Methods validated? ▪ Instruments (calibration)? ▪ Calibration gases (certificates, procedure)? ▪ OOS? ▪ Are filled cylinders quarantined before release? ▪ Who is authorised to release? ▪ Procedure (who and how)? ▪ Are there appropriate alert and action limits set to see process deviations on time (e.g. for water content)?	
5.7	Distribution		▪ Do distribution records provide traceability? ▪ Are cylinders adequately protected during transport?	GMP Annex 6, 7

	Area of operation/Items	Items	Questions to consider

6. ADDENDUM ON THE MANUFACTURE OF MEDICINAL GASES AT HOSPITALS

6.			
6.1	Responsibility	▪ Organisation chart, job descriptions ▪ Contracts? Manufacturing licences ▪ Responsibility of the pharmacy	▪ Who is responsible for the manufacturing and the distribution of medicinal gases in the hospital?
6.2	Premises and Equipment / Production	▪ Location management	▪ Who has access? How is access control organized? ▪ Drawings, List of equipment? ▪ Is production equipment released for use in manufacturing of medicinal gases (qualification report)?
6.3	Maintenance	▪ Maintenance ▪ Documentation	▪ How are the intervals for preventive maintenance determined? ▪ Outsourcing policy, acceptance (e.g. leakage tests)? ▪ How are measuring devices calibrated?
6.4	Inspection of the system	▪ Daily inspection e.g. pressure control and other critical parameters / areas	
6.5	Cleaning measures	▪ Premises and equipment	▪ For pipelines and storage tanks normally cleaning is not necessary; if there are any critical cleaning measures, they have to be validated) ▪ Storage areas (cylinders) clean and tidy?
6.6	Medicinal (compressed) Air	▪ Air inlet	▪ Source, contamination, filtration? ▪ Are there specifications for the porosity and material of the filter?
		▪ Compressor room condition	▪ Hygiene, temperature, ventilation, clean and tidy?
		▪ Pipeline system ▪ Pressure and temperature	▪ Are pipelines colour coded; is the coding standardized in a written procedure? ▪ Is there a SOP for purging of pipelines?
		▪ Filters	▪ Are design, size and sequence of the filters suitable? ▪ Pre, final, frequency of change, saturation, integrity? ▪ How are filters maintained (frequency of change, records)?
		▪ Contamination	▪ Is there a risk of contamination e.g. from the exhaust of the vacuum system of the hospital (often also situated in the compressor room)? ▪ Oil, water, other gases (as specified in the European Pharmacopoeia)?
		▪ Receiver vessels	▪ Material, condensation?
		▪ Dryer	▪ Alarm system, water traps? ▪ Online monitoring of dew point (water content)?

	Area of operation/Items	Items	Questions to consider
			▪ Are adsorption dryers used?
		▪ Pipelines	▪ Material, condition, welds and as plan?
		▪ Back-up system	▪ Is there a back-up system?
		▪ Capacity	▪ Is the capacity of the system sufficient?
6.7	Medicinal Oxygen		
		▪ Storage tank / evaporator unit	▪ Owner? ▪ History of equipment?
		▪ Back-up	▪ Is there a back-up system?
		▪ Delivery	▪ Dedicated mobile tank? ▪ CoA given by the supplier when delivered?
		▪ Filling procedure	▪ SOP, personnel of the hospital should be present, delivery has to be released before filling
		▪ Release of the medicinal product	▪ Who is responsible for the release after refilling of the storage tank?
		▪ Non-return valve	▪ There should be a validated method of backflow prevention in the line supplying the hospital to prevent contamination of the storage tank / evaporator unit.
6.8	Quality Control		
		▪ Test methods	
		▪ Specification	▪ Specification should be based on the European Pharmacopoeia
		▪ Validation of methods	▪ Especially, in the case of air, for the testing of oil (e.g. method has to be specific for the oil used for lubrication of the compressors)
		▪ Testing	▪ Identity, at least every delivery of raw materials, together with a qualified certificate of the supplier (if liquid oxygen is not delivered as a medicinal product)? ▪ Impurity (regular testing of the finished product, e.g. twice a year if the equipment is qualified and regular maintenance is accomplished)? ▪ Content (e.g. once a year in the case of oxygen)? ▪ Are samples of the finished products taken at the end of the pipeline? ▪ Bioburden (e.g. twice a year microbiological testing of the medicinal air, limit 10 cfu/m^3); ▪ Particles? ▪ OOS?

7. REVISION HISTORY

Date	Version number	Reasons for revision
25 September 2007	PI 025-2	Change in the Editor's co-ordinates

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